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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,214	KOCHENDOERFER, GERD G	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *16-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-15* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicant's election of the invention of Group I, claims 1-15, drawn to a method of producing a folded extramembranous receptor domain, a composition comprising a chemically synthesized extramembranous receptor domain and a kit comprising said composition in the reply filed on 12 December 2005 in response to the 29 August 2005 office action is acknowledged. Applicant has responded by electing the species "native chemical ligation". Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-46 are pending. Claims 16-46 have been withdrawn as directed to non-elected inventions. Claims 1-15 are under examination to the extent they read on the elected invention.

Claim Rejections

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a folded, extramembranous receptor domain of a membrane protein receptor wherein the extramembranous receptor domain is the extracellular, amino terminal domain of the glucagon-like peptide receptor (GLP-1 R), does not reasonably provide enablement for

a method of producing a folded receptor domain of a membrane protein receptor comprising any extramembranous receptor domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Claim 1, the independent claim of the instant invention, is broadly drawn to a method of producing a folded extramembranous receptor domain of a membrane protein receptor by forming a chemical ligation product, exposing said chemical ligation product to a folding buffer, and isolating a chemical ligation product that binds to a ligand of said extramembranous receptor domain of said membrane receptor protein. Claims 2-5 recite the further limitations of an extracellular domain (Claim 2), an amino-terminal domain (Claim 3), a receptor consisting of a G-protein coupled receptor (GPCR) or an enzyme-linked protein receptor (Claim 4) and a type B GPCR (Claim 5).

The specification defines extramembranous receptor domain to include "extracellular and cytosolic domains of a membrane protein receptor, or soluble portions of these domains that are capable of binding to a ligand of the membrane protein receptor, such as N-terminal and C-terminal extramembranous domains" (page 7, lines 32-33, bridging page 8, lines 1-3). The specification also discloses that the synthetic extramembranous receptor domain may have a segment that "includes an unnatural amino acid at a pre-selected residue position" (page 6, line 11). The specification also

teaches that a membrane protein receptor is a "receptor of a cell having at least one peptide segment capable of being embedded and anchoring the receptor in the lipid bilayer of a cell membrane" (page 8 lines 10-12). Examples of receptors taught by the specification are enzyme-linked receptors, cytokine receptors, GPCRs, and ion channel receptors (page 8, lines 13-22). The specification further discloses that polypeptides joined for ligation to produce the extramembranous receptor domain utilizing the methods of the claimed invention could be (1) totally synthetic; (2) semi-synthetic (produced at least partially by recombinant DNA technology; or (3) natural (produced *in toto* by ribosomal synthesis) (page 19, lines 15-18).

However, the specification teaches only the chemical ligation synthesis of the extracellular receptor domain of a Type B GLP-1 R GPCR. The working examples are all directed to just this particular folded extracellular domain of the receptor protein. Example 1 (page 29) discloses the peptide segments utilized for chemical synthesis of the GLP-1 receptor N-terminal domain (NTD) were synthesized using a peptide synthesizer following established protocols. Example 2 (page 31) teaches the native chemical ligation of the peptide segments synthesized by the methodology of Example 1 to form the full-length GLP-1R NTD. Folding of the full-length GLP-1R NTD is taught in Example 3 (page 32); the binding of GLP-1 to the synthesized extracellular receptor domain of the GLP-1 R GPCR is taught in Examples 6 (page 34) and 7 (page 35). The specification discloses general information as to selecting an extramembranous receptor domain, and techniques used to ligate the peptide or polypeptide segments (page 10, line 28, bridging page 13, line 8). It does not provide any structural or functional information as to the length of the amino acid segments, which amino acids should be present, the nature of the binding sites, or any other characteristics of an extramembranous receptor protein which would permit the skilled artisan to use the methodology of the instant invention to synthesize an extramembranous receptor domain that would retain the ability to bind a ligand of said membrane protein receptor. The skilled artisan would have to undertake undue experimentation to determine which other of the myriad numbers of membrane protein receptor molecules, disclosed in the

specification on page 8, could be utilized in the methods of the instant, claimed invention.

The art does not provide teachings that would compensate for these omissions in the specification. Muir et al (1998, PNAS 95:6705-6710) teach that "native chemical ligation has proven very useful for the total synthesis of small proteins and protein domains, but has not been extended to the synthsis of proteins beyond ~ 15 kDa" (page 6705, column 1, 2nd paragraph). Muir (2003, Annu. Rev. Biochem. 72:249-289) also teaches that expressed protein ligation has been applied to "kinases, phophatases, transcription factors, polymerases, ion channels, cytoplasmic signaling proteins and antibodies" (page 266, last paragraph), but is silent as to the use of this technique to synthesize binding domains of transmembrane receptors. Dawson et al (2000, Ann. Rev. Biochem. 69:923-60) lists only the GLP 1R N-terminal domain as a receptor protein prepared by total synthesis using native chemical ligation (page 941, Table 2). Furthermore, the GLP-1 receptor belongs to a subclass of receptors that share a relatively large N-terminal extracellular domain. This property may confer unique characteristics to the extracellular domain of the receptors. Wilmen et al (1996, FEBS Letters 398:43-47) teach that the isolated solubilized N-terminal part of the receptor competes for GLP-1 binding with the intact, wild-type receptor (page 44, column 2, paragraph 3.2 and page 45, Fig. 2) and that radiolabeled GLP-1 can be covalently attached to the N-terminal domain of the GLP-1 R (page 46, column 1, paragraph 3.4 and Fig. 4A) demonstrating direct physical interaction of both components. The skilled artisan would be unable to predict whether the isolated, extracellular domains of other membrane protein receptors have characteristics similar to that of the extracellular domain of the GLP-1 R and could be utilized in a manner similar to that of the GLP-1 receptor.

Due to the large quantity of experimentation necessary to identify which of the numerous membrane protein receptors could be used in the claimed methods, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to extracellular domains other than that of the GLP-1 R, the complex nature of the invention, the state of the prior art which establishes only the GLP

1R N-terminal domain as a receptor protein prepared by total synthesis using native chemical ligation, and the breadth of the claims which recite the use of any extramembranous receptor domain, including a cytoplasmic one, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-5, 7-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims recite a method of making a folded extramembranous receptor domain of a membrane protein that binds to a ligand of said extra membrane protein receptor. The claims do not require that the synthetic polypeptide retain any particular conserved structure, or other disclosed distinguishing feature. The claims are drawn to a genus of extramembranous receptor domain proteins that is defined only by its ability to bind the receptor's cognate ligand.

The claimed subject matter must be described in the specification to ensure that applicant had in his possession, as of the filing of the application, the specific subject matter claimed. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a requirement that utilization of the disclosed the synthetic method result in a molecule that retains the ability of binding a ligand that binds to the native receptor. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of receptor polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of synthesizing it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of producing a folded extramembranous receptor domain of GLP-1 R, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Objections

Claims:

Claim 1 is objected to because of the following informalities: the conclusionary statement of the claim recites "isolating from said folding buffer chemical ligation product". An "a" should be inserted so that the statement reads "isolating from said folding buffer a chemical ligation product". Appropriate correction is required.

Claim 6 is objected to as being dependent upon a rejected claim.

Claim 7 is objected to as reciting non-elected inventions. Appropriate correction is required.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

SHS

ELIZABETH KEMMERER
PRIMARY EXAMINER